Review Article

A Review of Management of the Obesity in Type-2 Diabetes Mellitus

Begum IA[1], Salakeen S[2], Islam MA[3], Anwar T[4], Jahan I[5], Yesmin F[5]

Abstract

Diabetes is a growing global health concern. More than 90% of patients with diabetes have overweight or obesity. Obesity affects all organ systems, causing increased rates of cardiovascular and renal disease, certain cancers, arthritis and sleep apnea. Whereas weight gain and obesity worsen insulin resistance, the elevated risk for diabetes complications in patients with obesity. The BMI is still used to classify overweight and obesity. Modest & sustain weight loss, reduces blood glucose, HbA1c, triacylglycerol & greater weight loss produces greater benefits, reducing the need for glucose-lowering agents, better blood pressure control and lipid control, slow complications of diabetes, and prevent the progression of prediabetes to type 2 diabetes. Weight loss can be achieved by lifestyle intervention (diet, exercise & behavior change), pharmacotherapy, or bariatric surgery, is highly effective as a primary interventional strategy in both the prevention and treatment of type 2 diabetes. Lifestyle modification can be an effective first step but integrated approach to weight management in the diabetic patient is recommended which helps to promote lifestyle modification for all patients. Dietary intervention can be achieved by a low-fat, low-carbohydrate, or the Mediterranean-style diet. For maintaining weight loss, in addition with dietary restriction, 200-300 min/week of physical activity recommended by American Diabetes Association (ADA). Drug therapy as an adjunct to lifestyle modifications for many obese patients who do not reach target weight loss with lifestyle modification alone. Drug therapy approved by Food and Drug Administration (FDA) may be short term & long term. Phentermine is indicated for short term use, Orlistat, Locarserin, Liraglutide are indicated for long term use, combination therapy Phentermine + Topiramite & Naltrexone + Bupropion also used in long term treatment. Metabolic Surgery includes Bariatric & Gastrectomies, should be a treatment options for those only after failed medical therapy- to reduce weight loss & to improve glycemic control.

Keywords: Diabetes, Obesity, BMI, Lifestyle Modifications, Pharmacotherapy & Metabolic Surgery

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Introduction

Type-2 diabetes mellitus (T2DM) is closely associated with obesity, primarily through the link of insulin resistance. 87.5% of those with T2DM have overweight or obesity; over 60% have a BMI ≥30. Obesity affects all organ systems, causing increased rates of cardiovascular and renal disease, certain cancers, arthritis and sleep apnea[1,2]. Patients with both type-2 diabetes and overweight or obesity who also have inadequate glycemic control, blood pressure and lipid control and/or other obesity-related medical conditions, lifestyle changes that result in modest and sustained weight loss produce clinically meaningful reductions in blood glucose, HbA1c, and triglycerides[3-8].

Greater weight loss produces even greater benefits, including reductions in blood pressure, improvements in LDL and HDL cholesterol and reductions in the need for medications to control blood glucose, blood pressure and lipids[7,8,14], and may result in achievement of glycemic goals in the absence of glucose-lowering agent use in some patients[9]. However, weight-loss benefits are progressive; more intensive weight-loss goals (>5%, >7%, >15%, etc.) may be pursued if needed to achieve a healthy weight and/or if the patient is more motivated and more intensive goals can be feasibly and safely attained. There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type-2 diabetes[4,5,6] and is beneficial in the treatment of type-2 diabetes[10-14].

The American Diabetes Association (ADA) recommends that patients with prediabetes lose 7% of baseline body weight to avoid developing diabetes[3]. Weight loss of as little as 2-5% produces

[1] Dr. Ismat Ara Begum, Associate Professor, Department of Biochemistry, Popular Medical College, Dhaka, Bangladesh.
[2] Dr. Sirajus Salakeen, Lecturer, Department of Biochemistry, Popular Medical College, Dhaka, Bangladesh.
[3] Dr. Md. Ashraful Islam, Assistant Professor, Department of Orthopedics, BSMMU, Dhaka, Bangladesh.
[4] Dr. Taznuva Anwar, Assistant Professor, Department of Biochemistry, Popular Medical College, Dhaka, Bangladesh.
[5] Dr. Iffat Jahan, Assistant Professor, Department of Physiology, Eastern Medical College, Cumilla, Bangladesh.
[6] Dr. Farzana Yesmin, Associate Professor, Department of Physiology, Popular Medical College, Dhaka, Bangladesh.

Address of Correspondence: Dr. Ismat Ara Begum, Associate Professor, Department of Biochemistry, Popular Medical College, Dhaka, Bangladesh. Mobile: +8801818518665, Email: dr_ismatara@yahoo.com

a clinically meaningful reduction in fasting blood glucose (20 mg/dL)[1] and weight loss of 5-10% of baseline body weight is recommended as an initial goal of treatment and this amount of weight loss is associated with a 0.6-1.0% reduction in HbA1c & numerous other health improvements[1].

The aim of this review study is to provide evidence-based recommendations for weight-loss therapy, including lifestyle intervention (diet, physical activity and behavior change), pharmacologic and surgical interventions, for obesity management as treatment for hyperglycemia in type-2 diabetes and to understand the benefits of weight reduction for control of glycaemia in diabetes.

Diagnosis of obesity

BMI can be calculated manually as weight divided by the square of height in meters or electronically using the electronic medical record or other resources. Once calculated, BMI should be classified to determine the presence of overweight or obesity, discussed with the patient, and documented in the patient record[15].

Patients with overweight or obesity that, in general, higher BMIs increase the risk of cardiovascular disease and all-cause mortality, as well as other adverse health and quality of life outcomes. Patient's readiness to engage in behavioral changes for weight loss and jointly determine weight-loss goals and patient appropriate intervention strategies[16].

Strategies may include dietary changes, physical activity, behavioral therapy, pharmacologic therapy and metabolic surgery (Table-I). The latter two strategies may be prescribed for carefully selected patients as adjuncts to diet, physical activity and behavioral therapy.

Table-I: Treatment options on the basis of BMI

Treatment	BMI 25-26.9	BMI 27-29.9	BMI ≥30
Lifestyle intervention	+	+	+
Pharmacotherapy		+	+
Surgery			+

Management of the obesity in Type-2 Diabetes Mellitus

A. Lifestyle intervention (Diet, Physical Activity and Behavioral Therapy)

Recommendations

a. Diet, physical activity, and behavioral therapy designed to achieve and maintain >5% weight loss is recommended for patients with type-2 diabetes who have overweight or obesity and are ready to achieve weight loss.

b. For patients who achieve short term (<3 months) weight-loss goals, long-term (≥1 year) body weight maintenance programs are recommended when available.

c. To achieve weight loss of >5%, short-term (3 month) interventions that use very low-calorie diets (≤800 kcal/day) and meal replacements may be prescribed for carefully by trained practitioners with close medical monitoring. To maintain weight loss, such programs must incorporate long-term comprehensive weight-maintenance counseling.

The treatment of obesity is always intimately linked to the reduction of body weight. This can be achieved via different weight loss strategies, including lifestyle interventions (diet, physical activity and behavioral therapy), pharmaceutical interventions or bariatric surgery[16].

The Action for Health in Diabetes (Look AHEAD) trial did not show that an intensive lifestyle intervention reduced cardiovascular events in adults with type-2 diabetes and overweight or obesity[17], it did show the feasibility of achieving and maintaining long-term weight loss in patients with type-2 diabetes.

In the Look AHEAD intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years[18]. Approximately 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight and 27% lost and maintained ≥10% of their initial body weight at 8 years[18].

Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document other benefits of weight loss in patients with type-2 diabetes, including improvements in mobility, physical and sexual function and health-related quality of life[3,19].

Significant weight loss can be attained with lifestyle programs that achieve a 500-750 kcal/day energy deficit, which in most cases is approximately 1,200-1,500 kcal/day for women and 1,500-1,800 kcal/day for men, adjusted for the individual's baseline body weight. Weight loss of 3-5% is the minimum necessary for clinical benefit[20].

Diet

Dietary interventions may differ in the types of foods they restrict but are effective if they create the necessary energy deficit[21,22]. This can be achieved either by a low-fat, low-carbohydrate or the Mediterranean-style diet[23-25]. The latter one is characterized by its beneficial metabolic effects as well as by its delayed need for an antihyperglycemic drug therapy in the patients with newly diagnosed type-2 diabetes mellitus[26].

Additionally, the replacement of one or two meals per day by dietary supplements (low-calorie diets) might contribute to a nutritionally well-balanced diet and maintain weight loss[27]. Meal replacement plans prescribed by trained practitioners, with close patient monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, use of a partial meal replacement plan was associated with improvements in diet quality[28]. The diet choice should be based on the patient's health status and preferences, including a determination of food availability and other cultural circumstances that could affect the dietary patterns[29].

Exercise

Exercise is the key component of every lifestyle intervention. Especially aerobic exercise is the best mode to reduce fat mass. Moreover, an increase in physical activity reduces intra-abdominal fat, increases lean mass, decreases depression and improves glucose tolerance, insulin sensitivity and physical fitness. The CDC does recommend that all adults, regardless of their weight or diabetes status, get 150 min/week of moderate aerobic activity and perform resistance exercise twice per week[30].

Although exercise is an important component of every effective weight loss strategy, several studies reported additive effects on weight loss when it is combined with an energy restricted diet. It is important to understand that reducing caloric intake is more effective at achieving initial weight loss than only increasing exercise[31,32]. Patients who made dietary changes alone lost 7 kg more at the 6-month follow-up than patients who added physical activity alone[32]. Physical activity remains important for maintaining weight loss but should not be the primary focus of behavioral change for weight loss.

Behavior change

Approaching discussions about weight loss with the 5 A's model for behavior change has been shown to increase patients' motivation to lose weight and improve their success at weight loss[33,34]. The 5 A's are an important framework regardless of whether clinicians will provide weight loss support in their practice or will be referring patients to a weight loss program (Table-II)[35].

Table-II: Behavior therapy descried by the 5A's model

1.Assess	• Assess the patients for obesity or overweight with metabolic risk factors • Assess for the patients' readiness and ability to make change at this time
2.Advise	• Advise patients about increased risks of cardiovascular disease with excess adiposity • Advise the patients of health benefits of weight loss and lifestyle modification
3.Agree	• Agree with patients on a quantifiable and achievable weight loss goal that will lead to health benefits (i.e., a goal of losing 5% of initial body weight in 6 months of duration)
4.Assist	• Assist patients in defining a weight management strategy (i.e., practice-based weight loss counseling vs. referral to a weight loss program)
5.Arrange	• Arrange follow-up to create a structure for accountability and feedback on progress

For maintaining weight loss, the ADA guidelines recommend that patients with diabetes be referred to a long-term (at least 1 year) weight maintenance program that involves at least monthly visits, at least weekly weight measurements, and at least 200–300 min/week of physical activity[3].

B. Pharmacotherapy

Recommendations

a. Weight-loss medications are effective as adjuncts to diet, physical activity and behavioral counseling for patients with type-2 diabetes and BMI ≥27.

b. Glucose-lowering medications for patients with type-2 diabetes and overweight or obesity, consider a medication's effect on weight & minimize medications for comorbid conditions that are associated with weight gain.

c. If the patient's response to weight loss medications is 5% weight loss after 3 months or if there are significant safety or tolerability issues at any time, the medication should be discontinued and alternative medications or treatment approaches should be considered.

It is important to consider the potential role of medicines that are approved for weight management as additional treatments for people with diabetes who wish to lose weight.

Medications associated with varying degrees of weight loss include metformin, α-glucosidase inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists and amylin mimetics. Metformin has been associated with a 3-kg weight loss[36,37].

In addition to being associated with a 3.7-kg weight loss, pramlintide can also lower the daily insulin requirements in patients with diabetes on insulin therapy[38]. GLP-1 receptor agonists have been associated with a 5.3-kg weight loss[39]. SGLT2 inhibitors can promote a 2.4-kg weight loss and lower insulin requirements[40-42]. Dipeptidyl peptidase-4 inhibitors are generally body weight neutral[40,41].

The agents, insulin secretagogues, thiazolidine-diones and insulin often cause weight gain. When possible, clinicians should attempt to reduce or find alternatives to common medications that can increase appetite and promote weight gain, including sedating antihistamines, steroids, some selective serotonin reuptake inhibitors, beta-blockers and most antipsychotic agents[43].

The US Food and Drug Administration (FDA) has approved medications for both short-term and long-term weight management as adjuncts to diet, exercise and behavioral therapy. Nearly all FDA approved medications for weight loss have been shown to improve glycemic control in patients with type-2 diabetes and delay progression to type-2 diabetes in patients at risk[44]. Phentermine and other older adrenergic agents are indicated as short-term (≤12 weeks) treatment[45].

Five weight-loss medications are FDA approved for long-term use (more than a few weeks) by patients with BMI ≥27 with one or more obesity-associated comorbid condition (e.g., type-2 diabetes, hypertension, and/or dyslipidemia) who are motivated to lose weight[44].

Medications approved by the FDA for the treatment of obesity are summarized in Table-III. The rationale for weight-loss medication use is to help patients to more consistently adhere to low-calorie diets and to reinforce lifestyle changes. These medications are contraindicated in women who are pregnant or actively trying to conceive.

Most individuals with type-2 diabetes require combination therapy for weight management as the condition progresses. Many of them are initially started on metformin, the most suitable combinations for dual therapy where weight loss is important are metformin + SGLT2 inhibitor and metformin + GLP-1 RA. If triple therapy is needed, then the combination of metformin + SGLT2 inhibitor + DPP-IV inhibitor would seem suitable[46].

Table-III: Medication approved by FDA for treatment of obesity

Treatment options and Medications	Mechanism of action	Effect	Daily Dose	Weight loss % from baseline	HbA1C change %
Short term ≤12 weeks					
Phentermine	Appetite suppressant	Decrease appetite	8- 37.5 mg	1.2-6.1	
Long term >12 weeks					
Orlistat	Intestinal lipase inhibitor	Decrease fat absorption	60-120 mg tds	5.6-9.6	-0.69%
Lorcaserin	Serotonin receptor agonist	Decrease appetite	10 mg bd	4.5	-0.9%
Phentermine/ Topiramate	Sympathomimetic/ antiepileptic combination	Decrease appetite	7.5 mg/ 46 mg daily	7.8-9.8	0.4%
Naltrexone/ bupropion	Opiate antagonist/ antidepressant combination	Decrease appetite	8 mg/90 mg to 16 mg/180 mg Daily	5.0	-0.6%
Liraglutide	GLP-1 RA	Decrease appetite	1.8 mg - 3 mg Daily	4.7-6.0	-0.6 to -1.8

Orlistat, liraglutide and naltrexone/ bupropion are approved in the USA and European union.
Lorcaserin and phentermine/ topiramate are only approved in the USA.
GLP-1 RA = glucagon like peptide-1 receptor agonist, tds = three time daily, bd = twice daily.

Weight gain is a significant problem for many who are treated with insulin. Nonetheless, despite the fact that both SGLT2 inhibitor and GLP-1 RAs have been shown to reduce insulin requirements, improve glycemic control and mitigate weight gain when added to therapy for insulin-treated individuals. Current recommendations support continuation of metformin with insulin use, unless this is contraindicated[46].

C. Surgical management/ Metabolic surgery

Recommendations

a. Metabolic surgery should be recommended as an option to treat type-2 diabetes, with BMI ≥40 (BMI ≥37.5 in Asian Americans) and in adults with BMI 35.0-39.9 (32.5-37.4 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods.

b. Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in the management of diabetes and gastrointestinal surgery.

c. Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after surgery.

Several gastrointestinal (GI) operations including partial gastrectomy and bariatric procedures[47] promote dramatic and durable weight loss and improvement of type-2 diabetes in many patients. Given the magnitude and rapidity of the effect of GI surgery on hyperglycemia and experimental evidence that rearrangements of GI anatomy similar to those in some metabolic procedures directly affect glucose homeostasis[48], GI interventions have been suggested as treatments for type-2 diabetes and in that context, they are termed “metabolic surgery”.

A substantial body of evidence has now been accumulated, including data from numerous randomized controlled (nonblinded) clinical trials, demonstrating that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors in patients with type-2 diabetes and obesity compared with various lifestyle/ medical interventions[49,62].

Improvements in microvascular complications of diabetes, cardiovascular disease, and cancer have been observed only in nonrandomized observational studies[50-53]. Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality[49-52].

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g. <8 years)[54,55], nonuse of insulin, maintenance of weight loss and better glycemic control are consistently associated with higher rates of diabetes remission and/or lower risk of weight regain[54-56]. Beyond improving glycemia, metabolic surgery has been shown to confer additional health benefits in randomized controlled trials, including substantial reductions in cardiovascular disease risk factors[62], reductions in incidence of the microvascular disease[57] and enhancements in quality of life[55,58].

Metabolic surgery is more expensive than nonsurgical management strategies, but retrospective analyses and modeling studies suggest that metabolic surgery may be cost-effective or even cost-saving for patients with type-2 diabetes. However, results are largely dependent on assumptions about the long-term effectiveness and safety of the procedures[59,60].

Comparison of Drug and Bariatric (Metabolic) Therapies

Currently, bariatric therapies are more effective than drug therapies regarding weight reduction and metabolic processes - especially, when they are used to treat diabetes as demonstrated by the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial[60,61]. The current 5-year follow-up analysis of this trial supports their prior findings that bariatric surgery is superior to intensive medical therapy in terms of glycemic control, weight reduction, decreasing medication use (antidiabetic, antihypertensive and lipid-lowering agents) and improvement in quality of life. These beneficial effects were also observed among patients with mild obesity (BMI 27-34)[61,62].

Since bariatric surgery is almost excluded in this patient population, the promising results of the STAMPEDE trial raise the question if bariatric surgery should also be an approved therapeutic approach for patients with a BMI less than 35. However, further long-time cohort studies are needed. Unfortunately, anti-obesity agents have not been evaluated so far in patients who received bariatric surgery.

Conclusion

As obesity is an emerging epidemic of modern society, the co-incidence with diabetes is also emerging. Diabetes and overweight/ obesity are closely linked. Effective strategies for weight control include life style intervention, pharmacological and surgical interventions. Not all of these strategies are suitable for all obese type-2 diabetes patient. Attention should be drawn to concomitant therapies. Lifestyle intervention is

compulsory for all the obese patient of type-2 DM, pharmacotherapy is required if BMI >27, single therapy or combination therapy may indicated depend on the clinical assessment of the patient. Surgical treatment also indicated in some selected cases for obesity management. We have to reduce body weight in obese patient of type-2 diabetes to improve glycemic control, to slow the cardio-metabolic complications of diabetes and thereby improve morbidity & mortality of the patients.

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